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Pertussis Vaccination: Acellular Pertussis Vaccine for the Fourth and Fifth Doses of the DTP Series; Update to Supplementary ACIP Stat Recommendations of the Advisory Committee on Immunization Practices

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Summary

General recommendations on pertussis prevention were issued August 8, 1991, in the ACIP statement on diphtheria, tetanus, and pertussis (1). A supplementary statement on the use of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) was issued February 7, 1992 (2) after the licensure of ACEL-IMUNE (Registered), prepared by Lederle Laboratories. With the recent licensure of a second DTaP product, * Tripedia(Trademark), this statement updates the supplement. Tripedia(Trademark) has a formulation that differs from that of ACEL-IMUNE(Registered). Both DTaP vaccines are licensed for use only as the fourth and/or fifth doses of diphtheria, tetanus, and pertussis vaccination; they are not licensed for the initial three-dose series for infants and children, regardless of age. Whole-cell DTP should continue to be used for the initial three-dose series and remains an acceptable alternative for the fourth and fifth doses. For details on the background, indications, use, and precautions and contraindications of DTaP, refer to the earlier supplementary statement (2).

INTRODUCTION

Simultaneous vaccination against diphtheria, tetanus, and pertussis during infancy and childhood has been a recommended routine practice in the United States since the late 1940s. Whole-cell pertussis vaccines in the United States have been and continue to be prepared from suspensions of killed *Bordetella pertussis* whole bacterial cells. Routine vaccination with whole-cell vaccines has been highly effective in reducing the burden of disease and deaths due to pertussis (3). Whole-cell pertussis vaccines, although safe, are associated with a variety of expected adverse events; these concerns have led to attempts to develop safer pertussis vaccines that have high efficacy.

Several antigenic components of *Bordetella pertussis* have been identified. Candidate acellular pertussis vaccines, produced by multinational manufacturers, are now available due to advances in the methods of purifying and preparing these components. In general, these vaccines are immunogenic and are less likely to cause common adverse reactions than the current whole-cell preparations. Several clinical trials, which compare relative protective efficacy of primary vaccination utilizing diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccines with that of whole-cell vaccines administered to infants, are in progress or development. A lack of adequate evidence, until recently, to demonstrate the effectiveness of any single preparation has delayed U.S. licensure for any indication of a candidate acellular pertussis vaccine. On December 17, 1991, the Food and Drug Administration (FDA) licensed the DTaP vaccine ACEL-IMUNE (Registered) for use as the fourth and/or fifth doses of the recommended DTP series. The FDA has now licensed a second DTaP vaccine, Tripedia(Trademark).

Tripedia(Trademark) Information

On August 21, 1992, the FDA licensed Tripedia(Trademark) for use as the fourth and/or fifth doses of the recommended DTP series. The acellular pertussis vaccine components are purified from *Bordetella pertussis* by salt precipitation, ultracentrifugation, and ultrafiltration. After purification, filamentous hemagglutinin (FHA) and pertussis toxin (PT) are combined to obtain a 1:1 ratio and are then treated with formaldehyde to inactivate PT. Each dose of Tripedia(Trademark) contains 23.4 mcg protein of FHA and 23.4 mcg protein of inactivated PT (toxoid), as well as 6.7 Lf of diphtheria toxoid and 5.0 Lf of tetanus toxoid. The combined components are adsorbed to aluminum potassium sulfate and preserved with 1:10,000 thimerosal.

Household exposure and ecologic studies among Japanese children vaccinated at greater than or equal to 2 years of age, have suggested efficacy of the BIKEN and other acellular pertussis vaccines when combined with diphtheria and tetanus toxoids as DTaP (4-7). In addition, a randomized, placebo-controlled clinical efficacy trial in Sweden during the period 1985-1987 demonstrated efficacy when two doses of a BIKEN pertussis vaccine -- similar to the formulation in Tripedia(Trademark) -- were given to children starting at ages 5-11 months old, an age older than that recommended for initiating whole-cell DTP vaccination in the United States (1,8). However, the experiences in Sweden and Japan do not satisfactorily define whether acellular pertussis vaccines confer clinical protection when administered early in infancy (i.e., 2, 4, and 6 months of age) and whether protection induced at any age is equivalent to that of whole-cell pertussis vaccine preparations.

The following evidence supports the use of Tripedia(Trademark) after the initial three-dose series of whole-cell DTP vaccine in infants:

Immunogenicity

Antibody responses to PT and FHA following administration of Tripedia(Trademark) as the fourth and fifth doses of the vaccination series are similar to or higher than those following whole-cell DTP vaccine ([Table 1](#)). Data are available to demonstrate the immunogenicity of Tripedia(Trademark) among children ages 15-16 months. The standard, single-dose volume of Tripedia(Trademark) is 0.5 mL and should be administered intramuscularly (IM).

Clinical efficacy

The efficacy of two acellular pertussis vaccines developed by the Japan National Institute of Health (JNIH) and prepared by BIKEN was studied in 1985-1987 in a randomized, placebo-controlled clinical trial in Sweden (2,8). One of the vaccines (JNIH-6) contained 23.4 mcg protein/dose each of formaldehyde-treated PT and FHA. The first dose of vaccine or placebo was administered at 5-11 months of age; the second dose was administered 8-12 weeks later. For culture-confirmed disease with cough of any duration, the observed efficacy for JNIH-6 was 69% (95% confidence interval (CI), 47%-82%); for culture-confirmed pertussis with cough lasting greater than 30 days, the observed efficacy was 79% (95%

CI, 57%- 90%) (8). Non-blinded follow-up studies conducted over a 42-month interval after the trial had ended support the efficacy estimates obtained from the clinical trial (9).

Safety

Local reactions, fever, and other common systemic symptoms occur less frequently after receipt of Tripedia(Trademark) vaccine than after whole-cell DTP vaccine. In general, the frequency of local and common systemic events is approximately one-fifth to one-half the frequency of these events after whole-cell DTP vaccination ([Table 2](#)).

VACCINE USAGE

See the general ACIP statement on diphtheria, tetanus, and pertussis (1) and the supplementary statement on DTaP for more details (2). DTaP preparations are currently licensed only for use as the fourth and/or fifth doses of the DTP series among children ages 15 months through 6 years (before the seventh birthday). Any of the licensed whole-cell DTP or DTaP preparations can be used interchangeably for the fourth and fifth doses of the routine series of vaccination against diphtheria, tetanus, and pertussis among children greater than or equal to 15 months of age. The ACIP Committee recommends the use of DTaP, if readily available, because it substantially reduces local reactions, fever, and other common systemic events that often follow receipt of whole-cell DTP. There are no specific data to support the use of one particular DTaP vaccine product over the other. No data exist regarding the intermixed use of the two DTaP products at the fourth and fifth doses of the series with respect to safety, immunogenicity, or efficacy.

Tripedia(Trademark) can be administered to children as part of the recommended schedule of routine simultaneous vaccination with DTP; oral poliovirus vaccine (OPV); measles, mumps, and rubella vaccine (MMR); and, when appropriate, Haemophilus b conjugate vaccine (HbCV) at 15-18 months of age (9).

SIDE EFFECTS AND ADVERSE REACTIONS

For a complete discussion, see the general ACIP statement on diphtheria, tetanus, and pertussis and the supplementary statement on DTaP (1,2). Refer to the earlier supplementary statement for details on the precautions and contraindications to DTaP use (2).

Although mild systemic reactions such as fever, drowsiness, fretfulness, and anorexia occur frequently after both whole-cell DTP vaccination and Tripedia(Trademark) vaccination, they are less common after Tripedia(Trademark) ([Table 2](#)). These reactions are self-limited and can be safely managed with symptomatic treatment.

Moderate-to-severe systemic events, including fever greater than or equal to 40.5 C (105 F); persistent, inconsolable crying lasting greater than or equal to 3 hours; and collapse (hypotonic- hyporesponsive episode) have rarely been reported after vaccination with DTaP (8,10-12). Each of these events appears to occur less often than with whole-cell DTP. When these events occur after the administration of whole-cell DTP, they appear to be without sequelae; the limited experience with DTaP suggests a similar outcome.

Other more severe neurologic events, such as prolonged convulsions or encephalopathy, have not been reported in temporal association after administration of approximately 11,000 doses of Tripedia(Trademark) in U.S. studies. This limited experience does not allow conclusions to be drawn as to whether any rare serious adverse events will occur after administration of DTaP. Because DTaP causes fever less frequently than whole-cell DTP, it is anticipated that events such as febrile convulsions will be less common after receipt of DTaP.

- Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, prepared and distributed as Tripedia(Trademark) by Connaught Laboratories, Inc. (Swiftwater, Pennsylvania), was licensed August 21, 1992. The purified acellular pertussis vaccine component is produced by BIKEN/Tanabe

Corporation (Osaka, Japan), and is combined with diphtheria and tetanus toxoids manufactured by Connaught Laboratories.

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Table_1

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

Table 1. Comparison of immunologic responses to pertussis antigens in children vaccinated with Tripedia (TM) and in children vaccinated with whole-cell DTP given as the fourth DTP dose at 15-20 months of age and as the fifth DTP dose at 4-6 years of age *

Percentage with \geq 4-fold increase 30 days after vaccination at 15-20 months of age		Percentage with \geq 4-fold increase 30 days after vaccination at 4-6 years of age	
Tripedia (TM)	Whole-cell DTP	Tripedia (TM)	Whole-cell DTP

Assay	(N=354)	(N=175)	(N=211)	(N=65)

Pertussis toxin				
Enzyme immunoassay	92 +	50	89 +	55
Filamentous hemagglutinin				
Enzyme immunoassay	73 +	35	87 +	55
Agglutination &	72	91	NA @	NA @

* BIKEN Acellular DTP Vaccine-Bernstein H, et al. and unpublished data provided by the manufacturer. All children had been previously vaccinated with 3-4 doses of whole-cell DTP. Whole cell DTP, manufactured by Connaught, was used in the whole-cell comparison group.
+ P<0.05.
& Sample sizes for each group were 39 and 23, respectively.
@ NA -- not available.

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Table_2

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

Table 2. Comparison of frequency (%) of adverse events occurring within 72 hours following vaccination with Tripedia (TM) or whole-cell DTP in children given the fourth DTP dose at 15-20 months of age and the fifth DTP dose at 4-6 years of age *

Events	Vaccination at 15-20 months of age		Vaccination at 4-6 years of age	
	Tripedia(TM) (N=372)	Whole cell DTP (N=189)	Tripedia(TM) (N=240)	Whole cell DTP (N=76)

Local				
Any erythema	18 +	29	31 &	61
Erythema > 2.5 cm	3 &	13	18 &	47
Any induration	11 &	40	28 &	59
Induration > 2.5 cm	2 &	14	NA @	NA @
Pain/tenderness	14 &	77	46 &	93
Systemic				
Fever >= 38 C (100.4 F) **	20 &	44	7 &	22
Fever >= 39 C (102.2 F) **	1 ++	6	1	1
Drowsiness	12 &	33	15 +	33
Fretfulness	21 &	68	16 &	45
Vomiting	2	3	1.7	1.3

* BIKEN Acellular DTP Vaccine-Bernstein H, et al. and unpublished data provided by the manufacturer. All children had been previously vaccinated with 3-4 doses of whole-cell DTP. Whole-cell DTP, manufactured by Connaught, was used in the whole-cell comparison group.
+ P<0.05.
& P<0.001.
@ NA -- not available.
** Sample sizes for fever were 361, 186, 209, and 67, respectively.
++ P<0.01.

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